

## BREAKING ADVANCES

- 3173 | **Highlights from Recent Cancer Literature**

## REVIEW

- 3175 | **Considerations for the Clinical Application of Chimeric Antigen Receptor T Cells: Observations from a Recombinant DNA Advisory Committee Symposium Held June 15, 2010**  
Hildegund C.J. Ertl, John Zaia, Steven A. Rosenberg, Carl H. June, Gianpietro Dotti, Jeffrey Kahn, Laurence J.N. Cooper, Jacqueline Corrigan-Curay, and Scott E. Strome

## PRIORITY REPORTS

- 3182 | **STAT3 Inhibition Is a Therapeutic Strategy for ABC-like Diffuse Large B-Cell Lymphoma**  
Anna Scuto, Maciej Kujawski, Claudia Kowolik, Ludmila Krymskaya, Lin Wang, Lawrence M. Weiss, David DiGiusto, Hua Yu, Stephen Forman, and Richard Jove

*Précis:* Findings establish that STAT3 is essential to maintain the pathophysiology of an aggressive form of B cell lymphoma and they offer a preclinical proof of concept for STAT3 inhibition as a therapeutic approach to treat this cancer.

- 3189 | **The ABL Switch Control Inhibitor DCC-2036 Is Active against the Chronic Myeloid Leukemia Mutant BCR-ABL<sup>T315I</sup> and Exhibits a Narrow Resistance Profile**

Christopher A. Eide, Lauren T. Adrian, Jeffrey W. Tyner, Mary Mac Partlin, David J. Anderson, Scott C. Wise, Bryan D. Smith, Peter A. Petillo, Daniel L. Flynn, Michael W.N. Deininger, Thomas O'Hare, and Brian J. Druker

*Précis:* A third generation drug can overcome an acquired mutation in BCR-ABL that confers resistance to all currently approved targeted therapies for CML, addressing a critical unmet need to control drug resistance in this disease.

- 3196 | **Metformin Decreases the Dose of Chemotherapy for Prolonging Tumor Remission in Mouse Xenografts Involving Multiple Cancer Cell Types**

Dimitrios Iliopoulos, Heather A. Hirsch, and Kevin Struhl

*Précis:* Preclinical findings suggest that combining the diabetes drug metformin with standard chemotherapy prolongs remission in multiple contexts, and may allow chemotherapy doses to be lowered in patients.

## CLINICAL STUDIES

- 3202 | **Ribonucleotide Reductase Small Subunit M2B Prognoses Better Survival in Colorectal Cancer**

Xiyong Liu, Lily Lai, Xiaochen Wang, Lijun Xue, Sofia Leora, Jun Wu, Shuya Hu, Keqiang Zhang, Mei-Ling Kuo, Lun Zhou, Hang Zhang, Yafan Wang, Yan Wang, Bingsen Zhou, Rebecca A. Nelson, Shu Zheng, Suzhan Zhang, Peiguo Chu, and Yun Yen

*Précis:* This study defines a simple immunohistochemical marker the presence of which strongly prognoses better survival outcomes in colorectal cancer patients.

## MICROENVIRONMENT AND IMMUNOLOGY

- 3214 | **Adjuvant Combination and Antigen Targeting as a Strategy to Induce Polyfunctional and High-Avidity T-Cell Responses against Poorly Immunogenic Tumors**

Fernando Aranda, Diana Llopiz, Nancy Díaz-Valdés, José Ignacio Riezu-Boj, Jaione Bezunartea, Marta Ruiz, Marta Martínez, Maika Durantez, Cristina Mansilla, Jesús Prieto, Juan José Lasarte, Francisco Borrás-Cuesta, and Pablo Sarobe

*Précis:* Findings show how enhancing innate immunity with multiple adjuvant combination and improving T cell responses by targeted antigen strategies can elicit an effective immunotherapeutic response against poorly immunogenic tumors.

3225 **Aurora A is a Repressed Effector Target of the Chromatin Remodeling Protein INI1/hSNF5 Required for Rhabdoid Tumor Cell Survival**

SeungJae Lee, Velasco Cimica, Nandini Ramachandra, David Zagzag, and Ganjam V. Kalpana

*Précis:* High expression of the mitotic kinase Aurora A may underlie the aggressive behavior of rhabdoid tumors and findings suggest that targeting Aurora A may offer a rational therapeutic strategy to inhibit these tumors.

3236 **Novel Theranostic Opportunities Offered by Characterization of Altered Membrane Lipid Metabolism in Breast Cancer Progression**

Mika Hilvo, Carsten Denkert, Laura Lehtinen, Berit Müller, Scarlet Brockmüller, Tuulikki Seppänen-Laakso, Jan Budczies, Elmar Bucher, Laxman Yetukuri, Sandra Castillo, Emilia Berg, Heli Nygren, Marko Sysi-Aho, Julian L. Griffin, Oliver Fiehn, Sibylle Loibl, Christiane Richter-Ehrenstein, Cornelia Radke, Tuulia Hyötyläinen, Olli Kallioniemi, Kristiina Iljin, and Matej Orešič

*Précis:* This is the first study to describe the global changes in lipids that occur during breast cancer progression, highlighting new candidate prognostic markers and therapeutic targets in this important metabolic arena.

3246 **mTORC1 and mTORC2 Regulate EMT, Motility, and Metastasis of Colorectal Cancer via RhoA and Rac1 Signaling Pathways**

Pat Gulhati, Kanika A. Bowen, Jianyu Liu, Payton D. Stevens, Piotr G. Rychahou, Min Chen, Eun Y. Lee, Heidi L. Weiss, Kathleen L. O'Connor, Tianyan Gao, and B. Mark Evers

*Précis:* mTOR kinases regulate cell proliferation and survival but new connections to metastasis revealed here for the first time offer a mechanistic rationale for certain uses of dual mTOR inhibitors in settings of advanced cancer.

3257 **FOXO1 Inhibits Runx2 Transcriptional Activity and Prostate Cancer Cell Migration and Invasion**

Haijun Zhang, Yunqian Pan, Li Zheng, Chungyoul Choe, Bruce Lindgren, Eric D. Jensen, Jennifer J. Westendorf, Liang Cheng, and Haojie Huang

*Précis:* Mechanistic findings suggest a basis for understanding how prostate cancers metastasize to bone, a major site for disease progression in many patients.

3268

**The IL-8-Regulated Chemokine Receptor CXCR7 Stimulates EGFR Signaling to Promote Prostate Cancer Growth**

Rajendra Kumar Singh and Bal L. Lokeshwar

*Précis:* Findings suggest that pro-inflammatory cytokine IL-8, which is elevated in the microenvironment of many tumors, may stimulate tumor cell growth in part through increasing expression of a chemokine receptor that colocalizes with EGFR and activates EGFR signaling.

3278

**Association of Specific Genotypes in Metastatic Suppressor HTPAP with Tumor Metastasis and Clinical Prognosis in Hepatocellular Carcinoma**

Ning Ren, Jin-Cai Wu, Qiong-Zhu Dong, Hai-Jing Sun, Hu-Liang Jia, Guo-Cai Li, Bing-Sheng Sun, Chun Dai, Jiong Shi, Jin-Wang Wei, Yuan-Yuan Sheng, Hai-Jun Zhou, Qing-Hai Ye, and Lun-Xiu Qin

*Précis:* Findings identify an HTPAP genotype and associated gene expression pattern that favors metastasis progression and that could be used to predict tumor metastasis and prognosis in HCC patients.

**PREVENTION AND EPIDEMIOLOGY**

3287

**Large-scale Exploration of Gene-Gene Interactions in Prostate Cancer Using a Multistage Genome-wide Association Study**

Julia Ciampa, Meredith Yeager, Laufey Amundadottir, Kevin Jacobs, Peter Kraft, Charles Chung, Sholom Wacholder, Kai Yu, William Wheeler, Michael J. Thun, W. Ryan Divers, Susan Gapstur, Demetrius Albanes, Jarmo Virtamo, Stephanie Weinstein, Edward Giovannucci, Walter C. Willett, Geraldine Cancel-Tassin, Olivier Cussenot, Antoine Valeri, David Hunter, Robert Hoover, Gilles Thomas, Stephen Chanock, and Nilanjan Chatterjee

*Précis:* A large genome-wide study that incorporated modern analytic methods highlights some provocative genetic interactions with established susceptibility loci that may help elucidate roots of prostate cancer susceptibility.

3296 **A Simple Approach to Cancer Therapy Afforded by Multivalent Pseudopeptides That Target Cell-Surface Nucleoproteins**

Damien Destouches, Nicolas Page, Yamina Hama-Kourbali, Valérie Machi, Olivier Chaloin, Sophie Frechault, Charalampos Birmpas, Panagiotis Katsoris, Julien Beyrath, Patricia Albanese, Marie Maurer, Gilles Carpentier, Jean-Marc Strub, Alain Van Dorselaer, Sylviane Muller, Dominique Bagnard, Jean Paul Briand, and José Courty

*Précis:* This interesting study defines a non-cytotoxic molecule that can efficiently localize to tumors, exert an antiangiogenesis activity, and selectively induce cancer cell death.

3306 **Inhibition of HIF Prolyl Hydroxylase-2 Blocks Tumor Growth in Mice through the Antiproliferative Activity of TGFβ**

Anne Klotzsche-von Ameln, Antje Muschter, Soufiane Mamlouk, Joanna Kalucka, Ina Prade, Kristin Franke, Maryam Rezaei, David M. Poitz, Georg Breier, and Ben Wielockx

*Précis:* Mechanistic findings deepen understanding of the anti-proliferative effects of TGFβ, offering new insights into the interaction of several crucial growth signaling pathways and suggesting possible therapeutic targets.

3317 **Polo-Like Kinase Plk2 Is an Epigenetic Determinant of Chemosensitivity and Clinical Outcomes in Ovarian Cancer**

Nelofer Syed, Helen M. Coley, Jalid Sehouli, Dominique Koensgen, Alexander Mustea, Peter Slozarek, Iain McNeish, Sarah P. Blagden, Peter Schmid, David P. Lovell, Eleftheria Hatzimichael, and Tim Crook

*Précis:* Findings define a mitotic kinase as a key determinant of drug resistance in epithelial ovarian cancer, with important implications for improving the management of this often deadly disease.

3328 **High-Throughput RNAi Screening Reveals Novel Regulators of Telomerase**

Maria Antonietta Cerone, Darren J Burgess, Cristina Naceur-Lombardelli, Christopher J. Lord, and Alan Ashworth

*Précis:* Findings point to ERK8 and other kinases that modulate telomerase activity as candidate therapeutic targets to disrupt telomere maintenance in cancer.

3341 **Aberrant Expression of OX1 Receptors for Orexins in Colon Cancers and Liver Metastases: an Openable Gate to Apoptosis**

Thierry Voisin, Aadil El Firar, Magali Fasseu, Christiane Rouyer-Fessard, Véronique Descatoire, Francine Walker, Valérie Paradis, Pierre Bedossa, Dominique Henin, Thérèse Lehy, and Marc Laburthe

*Précis:* Findings suggest a new strategy to selectively and effectively eradicate metastatic, chemoresistant colon cancer cells.

3352 **Human Xeno-Autoantibodies against a Non-Human Sialic Acid Serve as Novel Serum Biomarkers and Immunotherapeutics in Cancer**

Vered Padler-Karavani, Nancy Hurtado-Ziola, Minya Pu, Hai Yu, Shengshu Huang, Saddam Muthana, Harshal A. Chokhawala, Hongzhi Cao, Patrick Secrest, Dinorah Friedmann-Morvinski, Oded Singer, Darius Ghaderi, Inder M. Verma, Yu-Tsueng Liu, Karen Messer, Xi Chen, Ajit Varki, and Richard Schwab

*Précis:* Findings define xeno-autoantibodies against a diet-derived sialoglycan antigen that may be a cancer biomarker and an immunotherapeutic target.

3364 **Targeting Tumor Hypoxia: Suppression of Breast Tumor Growth and Metastasis by Novel Carbonic Anhydrase IX Inhibitors**

Yuanmei Lou, Paul C. McDonald, Arusha Oloumi, Stephen Chia, Christina Ostlund, Ardan Ahmadi, Alastair Kyle, Ulrich auf dem Keller, Samuel Leung, David Huntsman, Blaise Clarke, Brent W. Sutherland, Dawn Waterhouse, Marcel Bally, Calvin Roskelley, Christopher M. Overall, Andrew Minchinton, Fabio Pacchiano, Fabrizio Carta, Andrea Scozzafava, Nadia Touisni, Jean-Yves Winum, Claudiu T. Supuran, and Shoukat Dedhar

*Précis:* Therapeutic targeting of a metabolic enzyme that promotes survival of hypoxic cancer cells may offer a mechanistically novel and effective way to block the growth of metastatic cancer cells.

## TUMOR AND STEM CELL BIOLOGY

3377 **Cdk2 is Required for Breast Cancer Mediated by the Low Molecular Weight Isoform of Cyclin E**

Said Akli, Carolyn S. Van Pelt, Tuyen Bui, Laurent Meijer, and Khandan Keyomarsi

*Précis:* Findings establish a requirement for Cdk2 in LMW-cyclin E mediated mammary tumorigenesis, arguing that human breast tumors overexpressing LMW-cyclin E are prime candidates for anti-Cdk2 therapy.

3387 **A Developmental Taxonomy of Glioblastoma Defined and Maintained by MicroRNAs**

Tae-Min Kim, Wei Huang, Richard Park, Peter J. Park, and Mark D. Johnson

*Précis:* Findings suggest the existence of at least five distinct forms of glioblastoma that each relate to distinct stages of neural stem cell differentiation, providing an expanded framework to understand disease pathogenesis in a human neurodevelopmental context.

3400 **Phosphoglucose Isomerase/Autocrine Motility Factor Mediates Epithelial-Mesenchymal Transition Regulated by miR-200 in Breast Cancer Cells**

Aamir Ahmad, Amro Aboukameel, Dejuan Kong, Zhiwei Wang, Seema Sethi, Wei Chen, Fazlul H. Sarkar, and Avraham Raz

*Précis:* Findings define a microRNA signaling node that links an important pathway of epithelial-mesenchyme transition to cell metabolism and survival pathways with pivotal roles in cancer.

3410

**ID4 Imparts Chemoresistance and Cancer Stemness to Glioma Cells by Derepressing miR-9\*-Mediated Suppression of SOX2**

Hye-Min Jeon, Young-Woo Sohn, Se-Young Oh, Sung-Hak Kim, Samuel Beck, Soonhag Kim, and Hyunggee Kim

*Précis:* This study connects key regulators of stem cell properties and chemotherapeutic drug resistance in brain cancer, with potential implications for improving treatment.

3422

**BRCA1 Counteracts Progesterone Action by Ubiquitination Leading to Progesterone Receptor Degradation and Epigenetic Silencing of Target Promoters**

Verónica Calvo and Miguel Beato

*Précis:* The findings of this important study may help explain why host mutations in the BRCA1 tumor suppressor exert a tissue specificity in preferentially elevating the risk of breast cancer.

## CORRECTIONS

3432

**Correction: Cytokine Receptor CXCR4 Mediates Estrogen-Independent Tumorigenesis, Metastasis, and Resistance to Endocrine Therapy in Human Breast Cancer**

3433

**Correction: Genome-Wide Analysis of Alternative Splicing in Medulloblastoma Identifies Splicing Patterns Characteristic of Normal Cerebellar Development**

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## ABOUT THE COVER

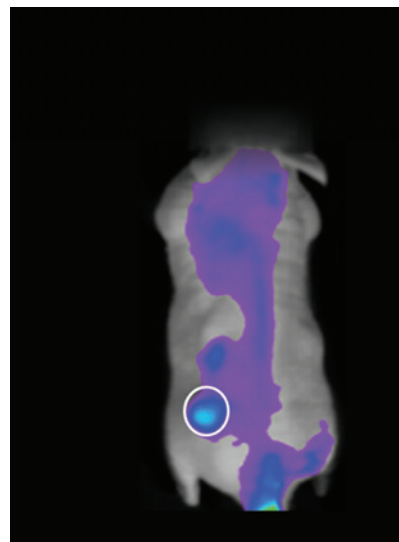
Several recent studies have demonstrated the involvement of cell-surface nucleolin in angiogenesis and tumor growth. In this study, we addressed the following questions:

Does N6L (or Nucant), a synthetic ligand of cell-surface nucleolin (nM range), block angiogenesis and tumor growth? What are its mechanisms of action, its bio-distribution and finally does it target other cell surface nucleolin partner proteins?

The key findings of this study are that:

- N6L inhibits anchorage-dependent and independent growth of several tumor cell lines and blocked angiogenesis
- N6L inhibit, *in vivo* tumor growth in a number of mouse subcutaneous human xenograft models
- N6L bio-distribution studies indicate that N6L rapidly localizes selectively in tumor tissue (see cover figure)
- N6L is a pro-apoptotic molecule, as demonstrated by *in vivo* as well as *in vitro* experiments
- Pull-down experiments and mass-spectrometry analysis have confirmed that nucleophosmin is a partner for nucleolin and also a target (nM range) for N6L

ImmuPharma group is currently developing N6L in Phase I/IIa clinical trials before initiating full efficacy studies in various indications as identified during this series of experiments. We believe that these findings pave the way for a novel approach of cancer treatment. For details, see the article by Destouches and colleagues on page 3296 of this issue.



# Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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